

# PATENT SPECIFICATION

NO DRAWINGS

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Date of Application and filing Complete Specification: 23 Dec., 1966.

No. 43667/69.

(Divided out of No. 1177956).

Complete Specification Published: 14 Jan., 1970.

Index at acceptance:—C2 C1E5K4, 1G5A, 1G5B, 1G6A2, 1G6B3, 1G6B4, 1G6B6, 1Q1A, 1Q6C, 1Q7A, 1Q8A, 1Q11B, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A8, 2A13, 2A14, 2R15, 2R18, 3A13C1C, 3A13C10B, 3A13C10H, B4A1, B4D, B4E, 213, 215, 22Y, 220, 227, 246, 247, 25Y, 250, 252, 255, 28X, 30Y, 305, 31Y, 313, 32Y, 323, 332, 34Y, 342, 351, 352, 36Y, 365, 593, 611, 62X, 620, 621, 662, 670, 671, 681, 708, 761, 170-189-276, 18X-195-275, KR, LP, ML; A5 B(38Y, 383, 392, 42Y, 420, 44Y, 442, 45Y, 451, 48Y, 480, 482, 51Y, 511, 54Y, 541, 542, 544, 55Y, 554, 556, 56Y, 565, 566, 57Y, 577, 61Y, 616, 67Y, 67X, 670)

International Classification:—C 07 d 87/54, 99/02

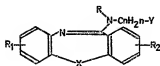
## COMPLETE SPECIFICATION

### Production of Oxazepines and Thiazepines

We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to a process for preparing 11-tertiary-aminodibenz [b,f] [1,4] oxazepines and thiazepines.

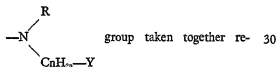
The oxazepines and thiazepines with which this invention is concerned may be represented by the formula:



(I)

wherein X is oxygen or sulfur; R<sub>1</sub> and R<sub>2</sub> are each hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>7</sub>-C<sub>22</sub>) alkoxy, halogen or trifluoromethyl; Y is hydroxy, amino, (C<sub>1</sub>-C<sub>6</sub>) alkylamino, di-(C<sub>1</sub>-C<sub>6</sub>) alkylamino, 1-piperazinyl, 4-(C<sub>1</sub>-C<sub>6</sub>) alkyl - 1 - piperazinyl, 4 - hydroxy (C<sub>1</sub>-C<sub>6</sub>) alkyl - 1 - piperazinyl, pyrrolidino, (C<sub>1</sub>-C<sub>6</sub>) alkyl-pyrrolidino, piperidino, (C<sub>1</sub>-

C<sub>6</sub>) alkylpiperidino, morpholino or (C<sub>1</sub>-C<sub>6</sub>) alkylmorpholino; R is (C<sub>1</sub>-C<sub>6</sub>) alkyl; n is 2, 3 or 4; or the

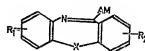


presents 1-piperazinyl, 4-(C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl, or 4-hydroxy (C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl.

The compounds of Formula I above are physiologically active on the central nervous system. They show high activity as tranquilizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation nor depression.

In accordance with this invention, compounds of Formula I are prepared by a process which comprises:

(a) reacting a compound of the formula:



(II)

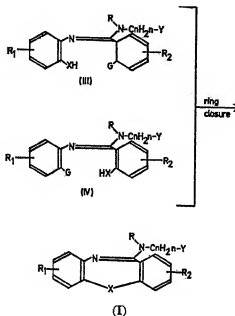
wherein each of R<sub>1</sub> and R<sub>2</sub> are as defined above, or is an amino or nitro group, X is



wherein  $R_1$ ,  $R_2$  and AM are as defined in relation to Formula II; F or G is hydroxy or mercapto and the other is halo, nitro or diazonium, and wherein F and G may occupy

interchanged positions; to form a heterocyclic ring wherein F and G together form an oxygen or sulfur atom.

More specifically, this process can be illustrated by the following ring closure reactions:



where  $R_1$ ,  $R_2$ ,  $X$ ,  $Y$  and  $n$  are as previously defined; and G is halogen or nitro. The ring closure reaction is achieved by heating the substituted N-(1,N-diarylimidoyl)-amine (intermediates III or IV) in an organic solvent. A polar solvent is generally employed to facilitate the reaction. Suitable solvents include formamide, dimethylformamide, dimethylacetamide, diethylacetamide, or diethylene-glycol monoethyl ether. The ring closure is usually carried out at an elevated temperature, conveniently the refluxing temperature of the solvent. Temperatures of from about 125°C. to about 200°C. are suitable, but the preferred temperature range is from about 150°C. to about 180°C. Heating is continued until the reaction is substantially complete, generally requiring from a few minutes to several hours or more.

In the above-described reaction, an alkaline condensing agent is preferably employed to promote ring closure in a reasonable period of time. Suitable condensing agents useful for these reactions are alkali or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate, or magnesium carbonate. Alkali metal hydroxides such as sodium hydroxide or potassium

hydroxide, may also be employed as alkaline condensing agents. Alkali metal hydrides and amides including sodium hydride, lithium amide, are also useful. These alkaline condensing agents are generally used in approximately equivalent molecular proportions with the N-(1,N-diarylimidoyl)-amine intermediates (III and IV). A metal catalyst may also be, optionally, employed to facilitate the ring closure reaction. Copper powder is particularly useful and copper salts are also successfully used.

As stated above, the compounds prepared by the process of the present invention are physiologically active on the central nervous system in that they show high activity as tranquilizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation nor depression.

A useful test for tranquilizer activity consists of measuring the reduction of spontaneous motor activity in animals by means of an actophotometer (a photoelectric device for quantitatively measuring locomotor activity). Graded doses of the active compounds prepared by the process of this invention are administered to groups of mice, and the effective dosage range for a significant reduction of motor activity (a measure of tranquilization) compared to control groups is established.

The anti-depressant properties of the compounds prepared by the process of the present invention are evident by measuring their ability to counteract a depression induced in animals by the administration of tetrabenazine hexamate. Graded doses of the active compounds are administered to groups of mice, and this is followed by administering a dose of tetrabenazine which is known to markedly depress the exploratory behavior of normal mice. The anti-depressant treated groups show normal exploratory behavior, while the control groups, and groups treated with an ineffective anti-depressant agent do not show this normal exploratory behavior, but show well known profound depression induced by tetrabenazine. The results from several dose levels are used to establish effective dose ranges. The anti-depressant compounds prepared by the process of this invention show their desirable properties by this procedure at dose levels which produce little or no untoward reactions, such as ataxia or reduced spontaneous motor activity.

In addition, some of the compounds prepared by the process of this invention show other valuable pharmaceutical properties, such as analgesic activity.

The compounds prepared by the process of this invention are, in general, white crystalline solids only slightly soluble in water, but moderately soluble in organic solvents such as methanol or ethanol. They are basic sub-

stances which are usually soluble in aqueous mineral acids at room temperature. They form substantially insoluble acid addition salts such as, for example, the hydrochloride, sulfate, phosphate, citrate, tartrate, maleate or fumarate. The active compounds, generally in the form of their salts, may be administered orally or parenterally and when so administered are effective central nervous system agents. For oral administration, the compounds prepared by the process this invention may be incorporated with the usual pharmaceutical excipients and used, for instance, in the form of tablets, capsules, dragees, liquids to be administered in drops, emulsions, suspensions and syrups, and in chocolate, candy or chewing gum. They may also be administered in aqueous solutions for parenteral injection.

The following examples illustrate in detail the preparation of representative 11-*tertiary*-aminodibenz[b,f] [1,4]oxazepines and thiazepines by the process of this invention

#### EXAMPLE 1

Preparation of 11-[Methyl(2-methylaminoethyl)amino]dibenz[b,f] [1,4]-oxazepine dihydrochloride

A mixture of 3 g. of 11-aminodibenz[b,f]-[1,4]oxazepine, 1 g. of ammonium chloride and 10 ml. of  $N,N'$ -dimethylethylenediamine is heated on the steam bath for about 48 hours. The mixture is then heated under reduced pressure, and the excess diamine is removed by distillation. The resulting residue containing the crude product, is dissolved in 100 ml. of cold 10% hydrochloric acid, and the acidic solution is extracted with ether to remove impurities. Neutralization of the aqueous layer by the addition of cold 10% sodium hydroxide precipitates the crude product, and the mixture is extracted with ether, the ether extracts are dried over sodium hydroxide pellets and concentrated. The resulting oil is purified by partition chromatography on diatomaceous silica, recovered as an oil, dissolved in ether, dried over potassium hydroxide pellets, filtered and treated with anhydrous hydrogen chloride. 11-[Methyl(2-methylaminoethyl)amino]dibenz[b,f] [1,4]oxazepine dihydrochloride (1.4 g.), melting point  $220^{\circ}$ — $225^{\circ}$ C., is obtained.

#### EXAMPLE 2

Preparation of 11-(4-Methyl-1-piperazinyl)dibenz[b,f] [1,4]oxazepine

A mixture of 5 g. of 11-dimethylaminodibenz[b,f] [1,4]oxazepine, 1.2 g. of ammonium chloride and 25 ml of 1-methylpiperazine is heated in an autoclave at  $175^{\circ}$ C. for 24 hours. Methanol (100 ml.) is added to the reaction mixture and the resulting solution is evaporated to an oily residue which contains the crude product. This mixture is taken up in 100 ml. of water, acidified with cold,

dilute hydrochloric acid (1N) and filtered to remove precipitated solid. Concentrated ammonium hydroxide solution is added to the acidic filtrate until the mixture remains alkaline, the aqueous suspension is extracted with ether, and the ether extracts are dried over potassium hydroxide pellets and evaporated. The resulting oily residue is purified by repeating the above procedure, dissolving the product in aqueous hydrochloric acid, filtering and reprecipitating with ammonium hydroxide. The product is thereby obtained as a semi-solid residue (1.9 g.) after evaporation of the dried ether extracts, and when further purified by chromatography on silica gel followed by crystallization from petroleum ether, 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine, melting point  $97^{\circ}$ — $98^{\circ}$ C., is obtained.

#### EXAMPLE 3

Preparation of 2-Chloro-11-(4-Methyl-1-piperazinyl)dibenz[b,f] [1,4]oxazepine

The general procedure of Example 2 is repeated. A mixture of 2-chloro-11-dimethylaminodibenz[b,f] [1,4]oxazepine hydrochloride and an excess of 1-methylpiperazine is heated in an autoclave at  $175^{\circ}$ C. for about 24 hours and the crude product is isolated. When purified and crystallized from petroleum ether, 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine, melting point  $108^{\circ}$ — $110^{\circ}$ C. is obtained.

#### EXAMPLE 4

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f] [1,4]thiazepine

The procedure of Example 1 is repeated. By heating 2 - chloro 11 - aminodibenz[b,f] [1,4]thiazepine with an excess of N-methylpiperazine, the product 2-chloro-11-(4-methyl - 1 - piperazinyl)dibenz[b,f] [1,4]thiazepine is obtained. The base melts at  $93^{\circ}$ C when recrystallized from petroleum ether.

#### EXAMPLE 5

Preparation of 11-(4-Methyl-1-piperazinyl)dibenz[b,f] [1,4]thiazepine

The procedure of Example 2 is repeated. By heating 11 - aminodibenz[b,f] [1,4]thiazepine with an excess of N-methylpiperazine and 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]thiazepine is obtained.

#### EXAMPLE 6

Preparation of 2-Chloro-11-(1-piperazinyl)dibenz[b,f] [1,4]thiazepine

When the procedure of Example 1 is repeated and 2 - chloro - 11 - aminodibenz[b,f] [1,4]thiazepine is heated with an excess of piperazine, the product 2-chloro-11-(1-piperazinyl) - dibenz[b,f] [1,4]thiazepine is obtained which melts at  $127^{\circ}$ — $133^{\circ}$ C. when recrystallized from benzene-hexane. The dihydrochloride melts at  $218^{\circ}$ C.

## EXAMPLE 7

Preparation of 2-Chloro-11-[4-(2-hydroxyethyl)-1-piperazinyl]-dibenz[b,f][1,4]thiazepine

- 5 Using the procedure of Example 1 and heating 2 - chloro - 11 - aminodibenz[b,f][1,4]thiazepine with an excess of N-(2-hydroxyethyl)piperazine, the product 2-chloro - 11 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl] - dibenz[b,f][1,4]thiazepine is obtained.

## EXAMPLE 8

Preparation of 2-Methyl-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]thiazepine

- 15 When the procedure of Example 1 is repeated and 11 - amino - 2 - methylidibenz[b,f][1,4]thiazepine is heated with an excess of N-methylpiperazine, the product 2-methyl - 1 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]thiazepine is obtained.

## EXAMPLE 9

Preparation of 2-Bromo-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 25 Repeating the procedure of Example 2 and heating 2 - bromo - 11 - ethylaminodibenz[b,f][1,4]oxazepine with an excess of N-methylpiperazine the product 2 - bromo - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f][1,4]oxazepine is obtained.

## EXAMPLE 10

Preparation of 2-Fluoro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 30 When the procedure of Example 1 is repeated and 11 - amino - 2 - fluorodibenz[b,f][1,4]oxazepine is heated with an excess of N-methylpiperazine, the product 2-fluoro-11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained. The corresponding fumarate melts at 204°—205°C when recrystallized from isopropanol.

## EXAMPLE 11

Preparation of 8-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 35 The procedure of Example 1 is repeated. By heating 2 - amino - 8 - chlorodibenz[b,f][1,4]oxazepine with an excess of N-methylpiperazine, the product 8-chloro-11-(4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained.

## EXAMPLE 12

Preparation of 11-(4-Methyl-1-piperazinyl)-2-trifluoromethylidibenz[b,f][1,4]-oxazepine

- 55 When the procedure of Example 1 is repeated and 11 - amino - 2 - trifluoromethyl - dibenz[b,f][1,4]oxazepine is heated with an excess of N-methylpiperazine, the product 11 - (4 - methyl - 1 - piperazinyl) - 2 - trifluoromethyl - dibenz[b,f][1,4]oxazepine is obtained. The fumarate melts at 215°—

216°C. when recrystallized from isopropanol.

## EXAMPLE 13

Preparation of 11-(4-methyl-1-piperazinyl)-8-trifluoromethylidibenz[b,f][1,4]-thiazepine

- 65 Using the procedure of Example 1 and heating 11 - amino - 8 - trifluoromethyl - dibenz[b,f][1,4]thiazepine with an excess of N-methylpiperazine, the desired product, 11-(4 - methyl - 1 - piperazinyl) - 8 - trifluoromethyl - dibenz[b,f][1,4]thiazepine is obtained.

## EXAMPLE 14

Preparation of 2-Methoxy-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 75 The procedure of Example 1 is repeated except that 11 - amino - 2 - methoxydibenz[b,f][1,4]oxazepine is heated with an excess of N-methylpiperazine to produce 2-methoxy-11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f][1,4]oxazepine.

## EXAMPLE 15

Preparation of 2,8-Dichloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 85 Using the procedure of Example 1 and heating 11 - amino - 2,8 - dichlorodibenz[b,f][1,4]oxazepine with an excess of N-methylpiperazine, the product 2,8 - dichloro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained.

## EXAMPLE 16

Preparation of 11-(1-Piperazinyl)dibenz[b,f][1,4]oxazepine

- 95 When the procedure of Example 1 is used and 11 - aminodibenz[b,f][1,4]oxazepine is heated with an excess of piperazine, the product 11 - (1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained which melts at 116°—117°C. when recrystallized from petroleum ether.

## EXAMPLE 17

Preparation of 2-Chloro-11-(1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 105 The general procedure of Example 1 is repeated. By heating 11 - amino - 2 - chlorodibenz[b,f][1,4]oxazepine with an excess of piperazine, the product 2 - chloro - 11 - (1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained. This base melts at 175°—176°C. when recrystallized from petroleum ether.

## EXAMPLE 18

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

- 115 2 - Nitrodibenz[b,f][1,4]oxazepine - 11 - (10H)one, prepared as described in the Preparation (below), in anhydrous benzene is allowed to react with phosphorus pentachloride. The mixture is refluxed until it becomes homogeneous, and an excess of dimethylamine is added. Refluxing is continued 120

until the reaction is substantially complete and 2-nitro-11-dimethylamino-dibenz[b,f][1,4]oxazepine is thereby obtained.

- 5 A mixture of 2-nitro-11-dimethylamino-dibenz[b,f][1,4]oxazepine, ammonium chloride and an excess of N-methylpiperazine is heated for about 48 hours, according to the general procedure of Example 1. The excess N-methylpiperazine is removed by distillation under reduced pressure and 2-nitro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine is obtained.

- 15 A solution of 0.35 grams of crude 2-nitro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine, prepared as described above, in 10 milliliters of 0.3 Normal hydrochloric acid is hydrogenated at atmospheric pressure over 3 milligrams of platinum oxide. The reduction requires about 3 hours when conducted with gentle warming from the magnetic stirring motor. When no more hydrogen is absorbed, the solution is treated with a little charcoal and filtered. The resulting pale yellow solution contains 2-amino-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine and is used in the next step without isolation.

- 20 The above solution is cooled to 0°-5°C. and treated with 52 milligrams of solid 95% sodium nitrite and 1 milliliter of concentrated hydrochloric acid. The cold solution is treated with an ice-cold solution of 90 milligrams of cuprous chloride in 1 milliliter of concentrated hydrochloric acid and then is stirred at room temperature to complete the gradual evolution of nitrogen gas. The solution is warmed to 60°C. to insure completion of the reaction, cooled and washed with ether. Five milliliters of concentrated ammonium hydroxide and 15 milliliters of hexane are added and the entire mixture is filtered before separation of the organic phase. The hexane solution is chromatographed on alumina and 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine is isolated from the eluate. This product melts at 108°-111°C. when recrystallized from hexane.

50 Preparation  
2-Nitrodibenz[b,f][1,4]oxazepine-11-(10H)-one

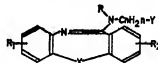
- 55 A solution of 8.05 grams of 2-chloro-5-nitrobenzoic acid in 10 milliliters of anhydrous tetrahydrofuran is treated with a solution of 7.9 grams of carbonyldiimidazole in 80 milliliters of tetrahydrofuran. The solution is heated under reflux for one half hour to complete evolution of the carbon dioxide formed and then treated with 4.36 grams of o-aminophenol in 30 milliliters of tetrahydrofuran. The solution is stirred at room temperature for 1 hour and refluxed for 15 minutes. The solvent is removed by distilla-

tion under reduced pressure and the residue is taken up in 80 milliliters of Normal sodium hydroxide in two portions. The solution is filtered with charcoal and the filtrate is treated with saturated ammonium chloride to precipitate 2-chloro-2'-hydroxy-5-nitrobenzanilide. The product melts at 191°-192°C. after recrystallization from the minimum amount of hot methanol diluted with an equal volume of 0.1 Normal hydrochloric acid.

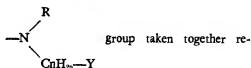
A solution of 5.85 grams of the above benzanilide in 20 milliliters of dimethylacetamide is treated with 2.7 grams of anhydrous potassium carbonate and the mixture is stirred and heated in an oil bath maintained at 180°C. for 5 minutes when the potassium carbonate has virtually all reacted. The mixture is cooled quickly and diluted with 20 milliliters of Normal sodium hydroxide and 100 milliliters of water. The precipitate is collected by filtration and recrystallized from about 500 milliliters of ethanol to yield 2-nitrodibenz[b,f][1,4]oxazepine-11-(10H)-one as very fine nearly colorless needles which melt at 260°-262°C.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula:



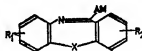
95 wherein X is oxygen or sulfur; R<sub>1</sub> and R<sub>2</sub> are each hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxy, halogen or trifluoromethyl; Y is hydroxy, amino, (C<sub>1</sub>-C<sub>6</sub>) alkylamino, di-(C<sub>1</sub>-C<sub>6</sub>) alkylamino, 1-piperazinyl, 4-(C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl, 4-hydroxy-(C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl, pyrrolidino, (C<sub>1</sub>-C<sub>6</sub>) alkyl-pyrrolidino, piperidino, (C<sub>1</sub>-C<sub>6</sub>) alkylpiperidino, morpholino or (C<sub>1</sub>-C<sub>6</sub>) alkylmorpholino; R is (C<sub>1</sub>-C<sub>6</sub>)alkyl; n is 2, 3, or 4; or the



presents 1-piperazinyl, 4-(C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl or 4-hydroxy-(C<sub>1</sub>-C<sub>6</sub>) alkyl-1-piperazinyl;

which process comprises:

- (a) reacting a compound of the formula:



wherein each of  $R_1$  and  $R_2$  is as defined above, or is an amino or nitro group, X is as defined above, and AM is amino,  $(C_1-C_6)$  alkylamino or  $di(C_1-C_6)$  alkyl-amino, with

5 an amine of the formula:



wherein  $R$ ,  $n$  and  $Y$  are as defined above, and (b) when required, after said amination, when at least one of  $R_1$  and  $R_2$  is amino, converting it into hydrogen,  $(C_1-C_6)$  alkoxy or halogen or when at least one of  $R_1$  and  $R_2$  is nitro, first converting it into amino

10 and then converting the amino group into hydrogen,  $(C_1-C_6)$  alkoxy or halogen.

15 2. A process according to Claim 1, wherein an excess of said amine is used in step (a).

3. A process according to Claim 1 or Claim 2, wherein said amination is carried out at a temperature of from 125° to 175°C.

4. A process according to Claim 1 and substantially as hereinbefore described.

5. An 11 - tertiary - aminodibenz[b,f] - [1,4] - oxazepine or thiazepine whenever prepared by a process according to any preceding claim.

6. A pharmaceutical preparation comprising a compound as defined in Claim 5, and a pharmaceutically acceptable carrier or diluent therefor.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.

Published by the Patent Office, 25, Southampton Buildings, London W.C.2, from which copies may be obtained